

## Bernard Fisher: A Pioneer Moves On

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On October 16, 2019, the breast cancer research community lost one of its greatest and most influential figures. Bernard Fisher—Bernie to friends—hailed from Pittsburgh, where he also trained and spent his entire life. A surgeon by training, he became interested in breast cancer and its basic biology early in his professional life. Soon after his faculty appointment at the University of Pittsburgh, he founded the Laboratory of Surgical Research and became one of the earliest examples of a physician-scientist. At the time, breast cancer was largely managed by the surgeons, and the reigning dogma was that en bloc resection of the primary tumor and known regional metastases was the optimal curative intervention. This operation, named the radical mastectomy, was the result of empiric development by multiple surgeons during the 19th century and its codification by William Halsted, a distinguished surgeon on the Johns Hopkins faculty, toward the 1890s. Although individual efforts were made throughout the next 70 years to develop alternative and less disfiguring interventions, the radical mastectomy remained the standard of care until the late 1970s. However, the lack of further progress during all those decades led to increased questioning of the need for such an intervention. Dr. Fisher's preclinical studies provided critical data, on which alternative scientific hypotheses were based, and eventually led to the development of clinical trials to test them.

Early in his career, he joined the National Surgical Adjuvant Breast and Bowel Project (NSABP) and in 1967 became Group Chair. Dr. Fisher was influenced by Thomas Kuhn and his book, *The Structure of Scientific Revolutions*, and the field was ready for major changes. His laboratory provided the science; the NSABP provided his clinical research tool. His contributions to our knowledge base led to multiple paradigm changes and, eventually, practice changes. The NSABP's earliest clinical trials focused on testing the value of adjuvant (perioperative and postoperative) chemotherapy. These trials, in retrospect, were timid attempts to test the hypothesis that breast cancer was a systemic disease from a very early stage in development and that chemotherapy administered around the time of definitive surgery would reduce the development of systemic metastases. Single agent chemotherapy was used (thio-TEPA), at a time when the most effective agents and combination therapy were not yet available. In addition, the trials included relatively modest numbers of patients and were thus hopelessly

underpowered. In all fairness, the randomized clinical trial was still in its infancy, and Fisher's research contributed to its further development, while benefiting from its implementation. Surprisingly, in retrospect, the first two NSABP trials of adjuvant chemotherapy provided modestly positive results and, therefore, proof of concept on which additional development was based.

Several subsequent generations of NSABP trials had a major impact in establishing the value of adjuvant chemotherapy for women with breast cancer of all ages, the superiority of combination chemotherapy over monotherapy, the value of endocrine therapy, the enhanced efficacy of combined endocrine and chemotherapy over endocrine therapy alone, the incremental benefit of taxanes over existing chemotherapy regimens, and the clinical utility of HER2-directed therapy with trastuzumab. Based on concepts developed by several leading breast cancer investigators, the NSABP developed a definitive clinical trial to establish the value of preoperative (or neoadjuvant) chemotherapy for breast cancer, a therapeutic model that is the preferred approach for several subtypes of breast cancer and an outstanding research approach to drug development.

Bernie Fisher's second major contribution was the demonstration that surgical interventions short of the radical mastectomy were equally efficacious in terms of overall survival: this approach evidenced the equivalence of a total mastectomy with the radical mastectomy and, later, the equivalence of the "lumpectomy" and radiotherapy with total mastectomy. These trials drove the rapid change in practice that, a few decades later, confirmed not only the equivalence but also the superiority of breast-conserving approaches to the more disfiguring, older surgical interventions.

A third major contribution of Dr. Fisher was the development of breast cancer prevention trials with endocrine therapy. Building on preclinical and clinical data from various investigators, the NSABP developed and implemented the NSABP P-1 trial, testing the efficacy of tamoxifen in reducing the risk of developing breast cancer. A highly positive trial, it led to NSABP P-2, comparing tamoxifen with raloxifene and, eventually, with the introduction of aromatase inhibitors to breast cancer prevention. Although these trials, in aggregate, provide compelling evidence in support of clinical cancer prevention, adoption by the public at large has been disappointing, at best.

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Perhaps the greatest practical contribution of Bernard Fisher to clinical science was the consolidation of NSABP as a highly productive clinical research group and the introduction of the clinical trial methodology to the surgical field. As a pioneer trialist, Dr. Fisher confronted and found solutions to the major challenges to the effective design and administration of large scale, multi-institutional, randomized studies, an experience that has taught the oncology field the value of careful oversight of quality control. All the important results of even his earliest NSABP trials have been verified by multiple subsequent analyses. At the time NSABP was founded, surgery was as much art as science, with each prominent surgeon advocating "his" technique as the optimal surgical intervention. To convince thousands of surgical specialists to conform to specific protocols to test scientific hypotheses was a superb achievement. This is perhaps the greatest demonstration of Dr. Fisher's leadership. Subsequent to his retirement as NSABP Chair, the Group continued to make significant contributions to the field of breast cancer research, cementing Dr. Fisher's legacy.

Dr. Fisher was clearly one of the foremost thought leaders in the breast cancer field throughout his career.

However, he largely limited his public comments, whether verbal or written, to evidence generated by his own laboratory research or clinical evidence derived from NSABP clinical trials. Widely respected and admired by all his colleagues, Dr. Fisher received numerous awards, prizes, and other forms of national and international recognition. His impact on the field was great, and his influence in changing the clinical management of breast cancer, definitive.

Married to his beloved wife, Shirley, Dr. Fisher was a private person who dedicated a major part of his focus and effort to his professional interests. However, he had other interests and was a well-read and informed person. He was an avid opera lover, and we shared many a performance in some of the major opera houses around the world.

Dr. Fisher's dedication, creativity, persistence, and leadership changed the field of breast cancer. We understand the disease and its treatments better today, thanks to his contributions, and our patients live longer and better because of his work. Future breast cancer researchers will see farther by standing on the shoulders of this giant.